

NO<sub>2</sub>, NH<sub>2</sub>, H, F, Cl, Br, I, COOH, OH, O-C<sub>1-6</sub> alkyl, SH, S-C<sub>1-6</sub> alkyl, CN, NH-C<sub>1-6</sub> alkyl, N(C<sub>1-6</sub> alkyl)<sub>2</sub>, CHO, C<sub>1-8</sub> alkyl, N<sub>3</sub>,

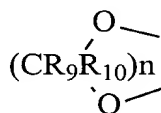
-Z-(CH<sub>2</sub>)<sub>a</sub>-N-((CH<sub>2</sub>)<sub>b</sub>OH)<sub>2</sub>, wherein Z is selected from the group consisting of O, NH and S, and a and b are each independently an integer of 2 or 3,

-Z-(CH<sub>2</sub>)<sub>a</sub>-N-(C<sub>1-6</sub> alkyl)<sub>2</sub> wherein Z is selected from the group consisting of O, NH and S, and a is an integer of 2 or 3,

-CH<sub>2</sub>NR<sub>4</sub>R<sub>5</sub>, where (a) R<sub>4</sub> and R<sub>5</sub> are, independently, hydrogen, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl-C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, hydroxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> COR<sub>6</sub> where R<sub>6</sub> is hydrogen, C<sub>1-6</sub> alkyl, perhalo-C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl-C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, hydroxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkyl, or (b) R<sub>4</sub> and R<sub>5</sub> taken together with the nitrogen atom to which they are attached form a saturated 3-7 membered heterocyclic ring which may contain a O, S or NR<sub>7</sub> group, where R<sub>7</sub> is hydrogen, C<sub>1-6</sub> alkyl, perhalo-C<sub>1-6</sub> alkyl, aryl, aryl substituted with one or more groups selected from the group consisting of C<sub>1-6</sub> alkyl, halogen, nitro, amino, C<sub>1-6</sub> alkylamino, perhalo-C<sub>1-6</sub> alkyl, hydroxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkyl and -COR<sub>8</sub> where R<sub>8</sub> is hydrogen, C<sub>1-6</sub> alkyl perhalo-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl, and aryl substituted with one or more C<sub>1-6</sub> alkyl, perhalo-C<sub>1-6</sub> alkyl, hydroxy-C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkyl groups;

R<sub>3</sub> is H; or

or R<sub>2</sub> and R<sub>3</sub> combine to form a ring



where R<sub>9</sub> and R<sub>10</sub> are each independently H or F and n is an integer of 1 or 2;

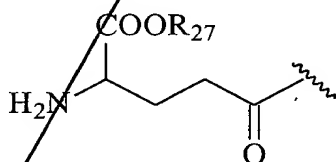
R<sub>11</sub> is H, or C(O)-(CH<sub>2</sub>)<sub>m</sub>-NR<sub>12</sub>R<sub>13</sub>, where m is an integer of 1-6 or

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cont  
AB

$-C(O)CHR_{14}NR_{12}R_{13}$ , where  $R_{14}$  is the side chain of one of the naturally occurring  $\alpha$ -amino acids,  $R_{12}$  and  $R_{13}$  are, independently, hydrogen,  $C_{1-8}$  alkyl or  $-C(O)CHR_{15}NR_{16}R_{17}$ , where  $R_{15}$  is the side chain of one of the naturally occurring  $\alpha$ -amino acids and  $R_{16}$  and  $R_{17}$  are each independently hydrogen or  $C_{1-8}$  alkyl;

$R_{18}$  is  $OR_{19}$  or  $R_{19}OC(O)-(CH_2)_m-NR_{20}$ , or  $R_{21}OC(O)CHR_{22}NR_{20}$ , where  $R_{19}$  is H or  $C_{1-6}$  alkyl,  $m$  is an integer of 1-6,  $R_{22}$  is the side chain of one of the naturally occurring  $\alpha$ -amino acids,  $R_{20}$  is hydrogen,  $C_{1-8}$  alkyl or  $-C(O)CHR_{23}NR_{24}R_{25}$ , where  $R_{23}$  is the side chain of one of the naturally occurring  $\alpha$ -amino acids and  $R_{24}$  and  $R_{25}$  are each independently hydrogen or  $C_{1-8}$  alkyl;

$R_{26}$  is H or



where  $R_{27}$  is H or  $C_{1-6}$  alkyl; and

X is S or O,

provided that  $R_{18}$  and  $R_{26}$  are not both H;

#### IN THE DRAWINGS

NE.

Please amend the figures as attached, the corrections being indicated in red ink.  
or a pharmaceutically acceptable salt thereof.--

#### SUPPORT FOR THE AMENDMENT

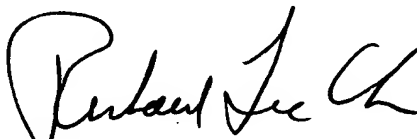
Support for the amendment to the title is found in the structure appearing on page 5, where, when X is a sulfur atom, describes a thioether linkage. Support for the amendment on

page 3 is the correction of an obvious typographical error, the appearance of which and the correction thereof being clear to those of ordinary skill in the art, since glutamic acid is an amino acid, while glutamate is the ester of glutamic acid. The correction to the structures on pages 5, , 10, 13, and in claim 1, is the correction of a typographical error and the correction is supported by the structure appearing on page 1, in which the nitrogen atom appears bridging the C and D rings. Further support is found in the structures of examples 3, 6 and 14 in which the bridging nitrogen atom is properly indicated. Support for the amendment to the structure of example 14, on page 34 is found in the title indicating that the substituent R is a cysteinylglycine. The proper structure of cysteinylglycine is now indicated. This is the correction of an obvious typographical error, the existence of which and the correction thereof being clear to those of ordinary skill in the art.

Applicants submit that this application is now in condition for examination on the merits and early notification of such action is earnestly solicited.

Respectfully submitted,

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IN THE TITLE OF THE INVENTION

Please amend the title as follows:

CAMPTOTHECIN COMPOUNDS WITH A [SULFHYDRYL] THIOETHER  
GROUP

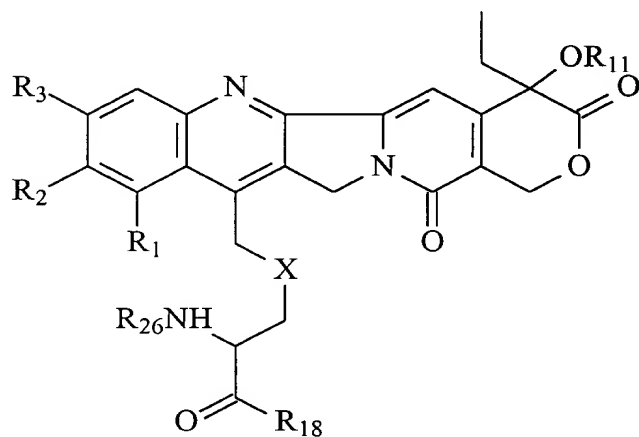
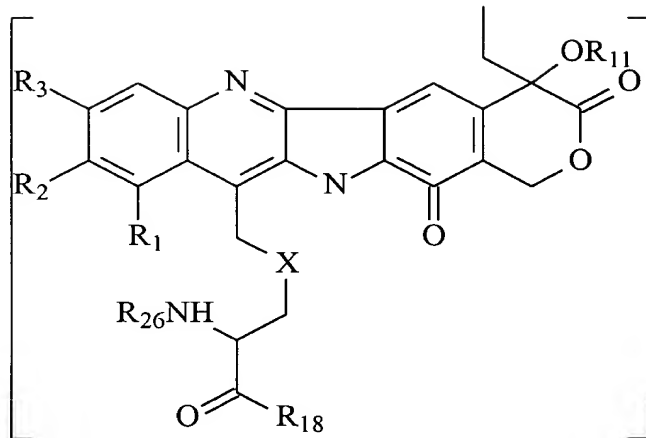
IN THE SPECIFICATION

Page 3, first full paragraph:

--Glutathione (Fig 2) is a tripeptide of [glutamate] glutamic acid, cysteine and glycine and found in high concentration in most normal cells and is often elevated in tumor tissue. In cancer cells, glutathione appears to play an important role in resistance to chemotherapy (Tew, 1994 #1038; Colvin, 1993 #628). For example, the chemotherapeutic alkylating agents such as cyclophosphamide, cisplatinum and BCNU are inactivated by covalent conjugation with glutathione to form thioether metabolites. This can occur spontaneously or through the action of the glutathione S-transferase enzymes. These transferases are often overexpressed in drug-resistant cells (Tew, 1994 #1038). Therefore glutathione conjugation results in chemical inactivation of the drug as well as increased export of the drug from the cell leading to resistance.--

Page 5, third full paragraph

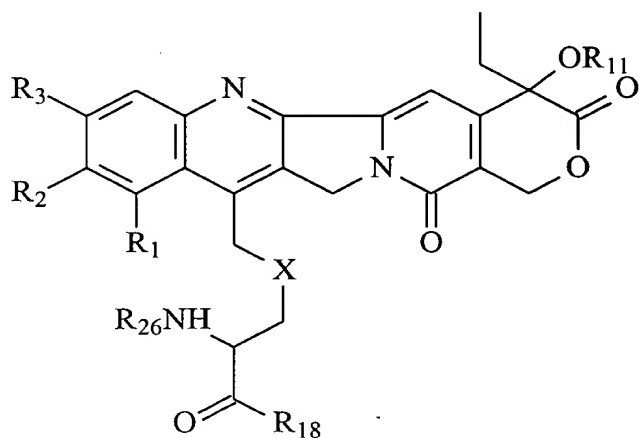
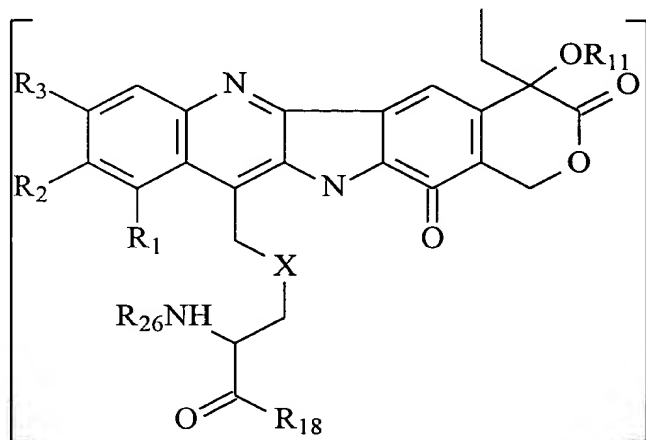
--These and other objects are made possible by the following camptothecin compounds which have combined topoisomerase I inhibiting and DNA-topoisomerase I cleavable complex stabilizing properties, of the formula



wherein R<sub>1</sub> and R<sub>2</sub>, are each independently--

Page 10, lines 5-7, first full paragraph,

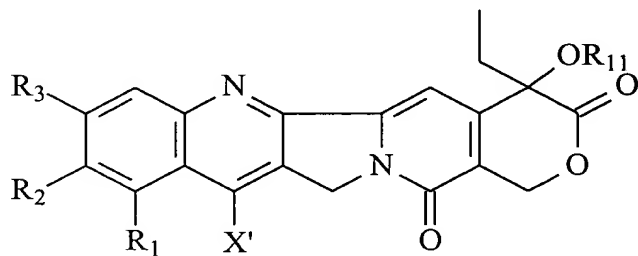
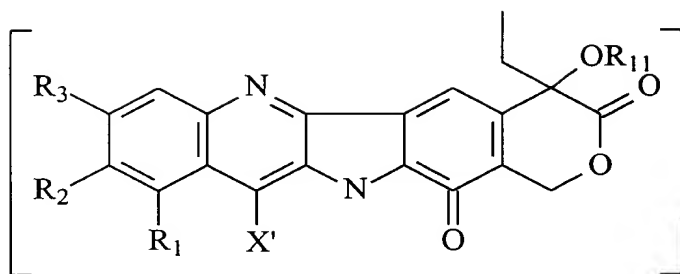
--The present invention is directed to a camptothecin compound



wherein R<sub>1</sub> and R<sub>2</sub>, are each independently--

Page 13, lines 7-12, second full paragraph,

Camptothecin compounds which may be used to form the conjugates of the present invention include 20(S)-CPT and derivatives thereof in which the A ring is unsubstituted or there is a substituent at the 9-, 10-, and 11-positions or a combination thereof or the 9- and 10,11-positions. Suitable compounds have the structure shown below:

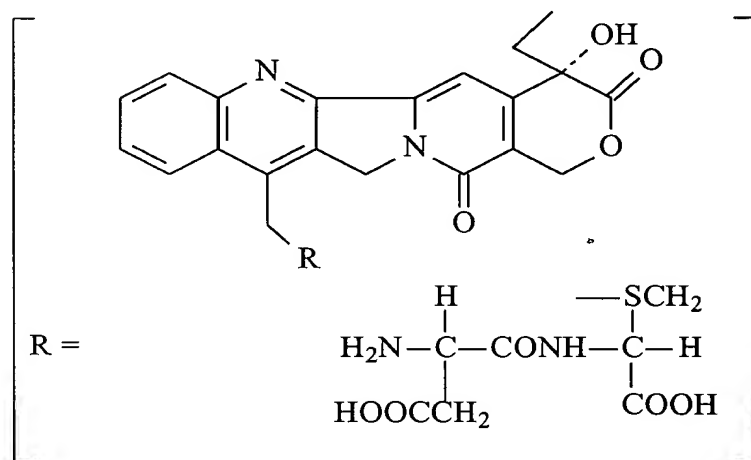


wherein  $R_1$  and  $R_2$ , are each independently--.

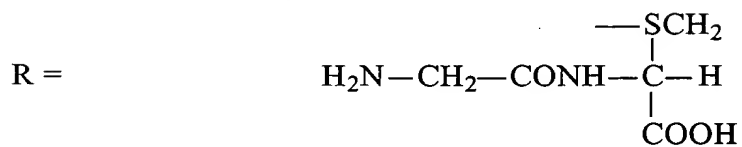
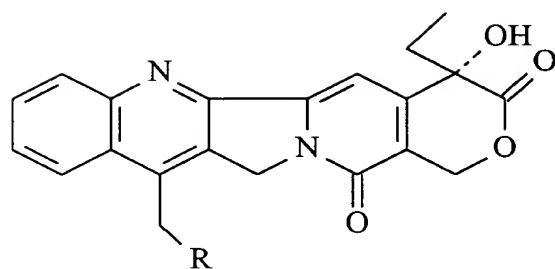
Page 34, Example 14,

Example 14

7-Cys-Gly-Methyl-20(S)-CPT



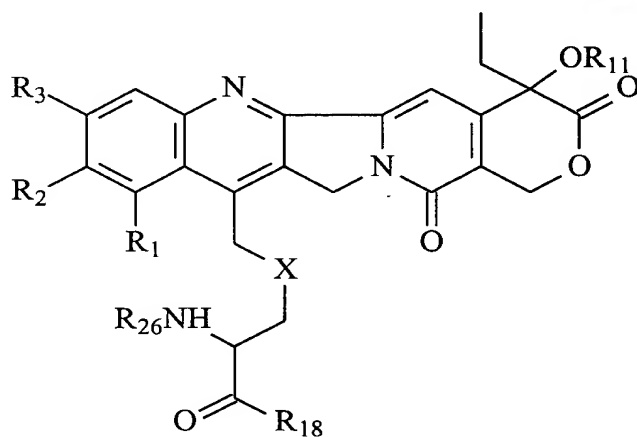
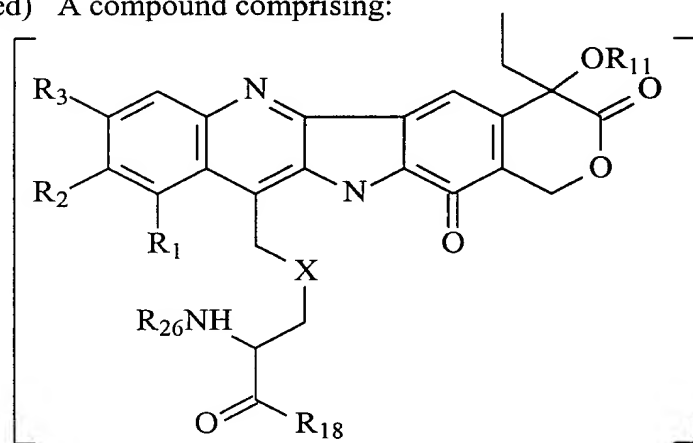




### IN THE CLAIMS

Please amend the claims as follows:

1. (Amended) A compound comprising:



wherein  $R_1$  and  $R_2$ , are each independently

$\text{NO}_2$ ,  $\text{NH}_2$ , H, F, Cl, Br, I,  $\text{COOH}$ , OH, O- $\text{C}_{1-6}$  alkyl, SH, S- $\text{C}_{1-6}$  alkyl, CN, NH- $\text{C}_{1-6}$  alkyl,  $\text{N}(\text{C}_{1-6} \text{ alkyl})_2$ ,  $\text{CHO}$ ,  $\text{C}_{1-8}$  alkyl,  $\text{N}_3$ ,

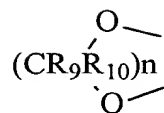
$-\text{Z}(\text{CH}_2)_a-\text{N}((\text{CH}_2)_b\text{OH})_2$ , wherein Z is selected from the group consisting of O, NH and S, and a and b are each independently an integer of 2 or 3,

$-\text{Z}(\text{CH}_2)_a-\text{N}(\text{C}_{1-6} \text{ alkyl})_2$  wherein Z is selected from the group consisting of O, NH and S, and a is an integer of 2 or 3,

$-\text{CH}_2\text{NR}_4\text{R}_5$ , where (a)  $\text{R}_4$  and  $\text{R}_5$  are, independently, hydrogen,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{3-7}$  cycloalkyl- $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl, hydroxy- $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$   $\text{COR}_6$  where  $\text{R}_6$  is hydrogen,  $\text{C}_{1-6}$  alkyl, perhalo- $\text{C}_{1-6}$  alkyl,  $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{3-7}$  cycloalkyl- $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl, hydroxy- $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$  alkyl, or (b)  $\text{R}_4$  and  $\text{R}_5$  taken together with the nitrogen atom to which they are attached form a saturated 3-7 membered heterocyclic ring which may contain a O, S or  $\text{NR}_7$  group, where  $\text{R}_7$  is hydrogen,  $\text{C}_{1-6}$  alkyl, perhalo- $\text{C}_{1-6}$  alkyl, aryl, aryl substituted with one or more groups selected from the group consisting of  $\text{C}_{1-6}$  alkyl, halogen, nitro, amino,  $\text{C}_{1-6}$  alkylamino, perhalo- $\text{C}_{1-6}$  alkyl, hydroxy- $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$  alkyl and  $-\text{COR}_8$  where  $\text{R}_8$  is hydrogen,  $\text{C}_{1-6}$  alkyl perhalo- $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy, aryl, and aryl substituted with one or more  $\text{C}_{1-6}$  alkyl, perhalo- $\text{C}_{1-6}$  alkyl, hydroxy- $\text{C}_{1-6}$  alkyl, or  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$  alkyl groups;

$\text{R}_3$  is H; or

or R<sub>2</sub> and R<sub>3</sub> combine to form a ring

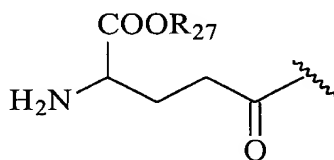


where R<sub>9</sub> and R<sub>10</sub> are each independently H or F and n is an integer of 1 or 2;

R<sub>11</sub> is H, or C(O)-(CH<sub>2</sub>)<sub>m</sub>-NR<sub>12</sub>R<sub>13</sub>, where m is an integer of 1-6 or  
-C(O)CHR<sub>14</sub>NR<sub>12</sub>R<sub>13</sub>, where R<sub>14</sub> is the side chain of one of the naturally occurring α-amino acids, R<sub>12</sub> and R<sub>13</sub> are, independently, hydrogen, C<sub>1-8</sub> alkyl or -C(O)CHR<sub>15</sub>NR<sub>16</sub>R<sub>17</sub>, where R<sub>15</sub> is the side chain of one of the naturally occurring α-amino acids and R<sub>16</sub> and R<sub>17</sub> are each independently hydrogen or C<sub>1-8</sub> alkyl;

R<sub>18</sub> is OR<sub>19</sub> or R<sub>19</sub>OC(O)-(CH<sub>2</sub>)<sub>m</sub>-NR<sub>20</sub>, or R<sub>21</sub>OC(O)CHR<sub>22</sub>NR<sub>20</sub>, where R<sub>19</sub> is H or C<sub>1-6</sub> alkyl, m is an integer of 1-6, R<sub>22</sub> is the side chain of one of the naturally occurring α-amino acids, R<sub>20</sub> is hydrogen, C<sub>1-8</sub> alkyl or -C(O)CHR<sub>23</sub>NR<sub>24</sub>R<sub>25</sub>, where R<sub>23</sub> is the side chain of one of the naturally occurring α-amino acids and R<sub>24</sub> and R<sub>25</sub> are each independently hydrogen or C<sub>1-8</sub> alkyl;

R<sub>26</sub> is H or



where R<sub>27</sub> is H or C<sub>1-6</sub> alkyl; and

X is S or O,

provided that R<sub>18</sub> and R<sub>26</sub> are not both H;--